UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/605,283	09/19/2003	Kapil N. Bhalla	1372.76.PRC	2282

21901 7590 05/27/2010

SMITH HOPEN, PA
180 PINE AVENUE NORTH
OLDSMAR, FL 34677

EXAMINER	
JAGOE, DONNA A	

ART UNIT	PAPER NUMBER
1619	

NOTIFICATION DATE	DELIVERY MODE
05/27/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PATENTS@SMITHHOPEN.COM
ajhopen@yahoo.com
PAIR@SMITHHOPEN.COM

Office Action Summary	Application No.	Applicant(s)	
	10/605,283	BHALLA ET AL.	
	Examiner	Art Unit	
	Donna Jagoe	1619	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 February 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19,23,26 and 27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19,23,26 and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 19, 23, 26 and 27 are pending in this application.

Applicants' arguments filed February 12, 2010 have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 19, 23, 26 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thiesing et al. et al. (Blood, 2002) and Virginia Commonwealth University, WO 02/22133 A1.

Thiesing et al. teach that chronic myelogenous leukemia (CML) is a hematopoietic stem cell disorder. In the chronic phase of the disease, there are excess numbers of myeloid cells (CML); however, these cells differentiate and function normally. Over time, there is a progressive loss of terminal differentiation and the disease terminates in an acute leukemia, known as blast crisis. Blast crisis is usually of a myeloid phenotype, but, in up to one third of patients, a lymphoid phenotype (ALL) is seen. Thiesing et al. teach that STI571 (imatinib mesylate) has shown significant activity in all phases of **CML** as well as Philadelphia chromosome positive acute leukemias (**ALL**) (page 3195, 1st paragraph). Thiesing et al teach that STI571's mechanism of action is to induce **apoptosis** of Bcr-Abl-expressing cell lines (page 3198, column 2). However, relapses with blast crisis patients treated with STI571 are a major problem and blast crisis patients are highly resistant to standard chemotherapy. Data suggest that combinations of STI571 with standard antileukemic agents are a

viable approach to the treatment of Bcr-Abl acute leukemias. Further, despite the dramatic results with the use of STI571 to treat patients with CML who have failed IFN therapy, it is questioned whether it will be possible to completely eradicate the leukemic clone as Bcr-Abl is thought to contribute to the genetic instability responsible for disease progression. Thiesing et al teach that **resistance would develop with long-term administration of STI571** and suggest the **combination** of STI571 with other agents to either prevent the emergence of resistant clones or to enhance the eradication of the leukemic clone (page 3199, columns 1-2). In both ALL and CML, Thiesing et al. teach that **STI571 should be supplemented with another agent known to treat leukemia**. Thiesing et al. does not teach supplementing STI571 with suberoylanilide hydroxamic acid.

Virginia Commonwealth University (hereafter referred to as VCU) teach co-administration of cyclin dependent kinase inhibitors with cellular differentiation agents to promote apoptosis in cancer cells (see abstract). Included in the agents that induce cellular differentiation are histone deacetylase inhibitors, such as suberoylanilide hydroxamic acid (SAHA) (page 4, lines 15-20). Leukemia is included in the types of cancer that is treatable with the combination (page 4, lines 24-26). Additionally, VCU teach that one agent alone (FP alone) had a minimal effect on apoptosis (see page 333, line 27 to page 34, line 3) and that the co-administration of a cyclin dependent kinase and a cellular differentiation agent (PMA and FP) resulted in a synergistic drug interaction (page 15, lines 16-21). VCU does not teach the combination of SAHA with the tyrosine kinase inhibitor, imatinib mesylate.

Both of the references teach that apoptosis occurs when each of the agents is contacted with the cells and each reference teach the combination with another agent known to treat leukemia.

Addressing the limitation of claim 19, drawn to contacting the living cells with the combination, simple administration of the agents would obviate claims drawn to contacting living cells.

Addressing the limitations of claim 19 wherein the combination is administered when the cancer cells are refractory to imatinib mesylate, Thiesing et al teach that resistance would develop with long-term administration of STI571 (imatinib mesylate) and teach that in both ALL and CML, **STI571 should be supplemented with another agent known to treat leukemia**. Further, VCU teach the combination of Histone Deacetylase Inhibitors (HDAC's), such as suberoylanilide hydroxamic acid (SAHA) with cyclin dependent kinases, another chemotherapeutic agent for leukemia.

Both references teach treatment of resistant leukemia and teach treatment with STI571 (Thiesing et al.) and SAHA (VCU) in the treatment of leukemia. It would have been obvious to one having ordinary skill in the art at the time the invention was make to employ the two agents imatinib mesylate and suberoylanilide hydroxamic acid for the induce apoptosis in cancer cells, such as chronic myelogenous leukemia, particularly when the cells become refractory to one agent alone.

Addressing the limitation of claim 23, drawn to cell exposure for about 48 hours, VCU teach that the combination of a cyclin dependent kinase and a histone deacetylase inhibitor are co-administered within the time range of 24-72 hours (page 11, lines 7-12)

which overlaps and encompasses the claimed 48 hours. Addressing instant claims 26 and 27, drawn to cell types of chronic myelogenous leukemia and acute lymphoblastic leukemia such as accelerated-phase cells and blast crisis phase cells, Thiesing et al. teach that STI571 (imatinib mesylate) has shown significant activity in all phases of **CML** as well as Philadelphia chromosome positive acute leukemias (**ALL**) (page 3195, 1st paragraph).

One having ordinary skill in the art could have combined SAHA and imatinib mesylate as claimed for the treatment of leukemia and in combination, each element would have performed the same function as it did separately and the results would have been predictable. Thus, it would be prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the references so as to have administered SAHA in combination with imatinib mesylate, as taught by both Thiesing et al. and VCU. One would have been motivated to do so because each of the therapeutic agents has been individually taught in the prior art to be successful at treating leukemia. Moreover, the instant situation is amenable to the type of analysis set forth in In re Kerkhoven, 205 USPQ 1069 (CCPA 1980) wherein the court held that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the very same purpose. The idea of combining them flows logically from having been individually taught in the prior art. Applying the same logic to the instant claims, one of ordinary skill in the art would have been imbued with at least a reasonable expectation of success that by administering the combination one would achieve a method for treating CML. The convenience of putting the histone deacetylase

inhibitor (e.g. SAHA) together with the tyrosine kinase inhibitor (e.g. imatinib mesylate) in one composition or method of treatment, though perhaps a matter of great convenience, did not produce a "new" or "different" function and to those skilled in the art, the use of the old elements in combination would have been obvious.

Response to Arguments

Applicant states that Thiesing does not teach inducing apoptosis in imatinib mesylate (STI571) refractory cells. In response, Thiesing et al teach that STI571's mechanism of action is to induce apoptosis of Bcr-Abl-expressing cell lines (page 3198, column 2). Thiesing et al. state that Bcr-Abl is thought to contribute to the genetic instability responsible for disease progression. Thiesing et al teach that **resistance would develop with long-term administration of STI571** and suggest the **combination** of STI571 with other agents to either prevent the emergence of resistant clones or to enhance the eradication of the leukemic clone (page 3199, columns 1-2). Applicant asserts that Thiesing does not teach a histone deacetylase inhibitor and assert that it cannot be predicted that the administration of STI571 with different agents cannot be predictive of synergistic or additive results. Both of the references teach that apoptosis occurs when each of the agents is contacted with the cells and each reference teach the combination with another agent known to treat leukemia. Applicant asserts that Thiesing does not teach supplementing STI571 with SAHA and VCU teaches administration of cyclin dependent kinase inhibitors with cellular differentiation agents to promote apoptosis in cancer cells and further asserts that instant claim 19 is

drawn to the administration of imatinib mesylate and SAHA. In response, one having ordinary skill in the art could have combined SAHA and imatinib mesylate as claimed for the treatment of leukemia and in combination, each element would have performed the same function as it did separately and the results would have been predictable. Thus, it would be prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the references so as to have administered SAHA in combination with imatinib mesylate, as taught by both Thiesing et al. and VCU. One would have been motivated to do so because each of the therapeutic agents has been individually taught in the prior art to be successful at treating leukemia. Moreover, the instant situation is amenable to the type of analysis set forth in In re Kerkhoven, 205 USPQ 1069 (CCPA 1980) wherein the court held that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the very same purpose. The idea of combining them flows logically from having been individually taught in the prior art. Applying the same logic to the instant claims, one of ordinary skill in the art would have been imbued with at least a reasonable expectation of success that by administering the combination one would achieve a method for treating CML. Applicant argues that the cyclin dependent kinases of VCU "oppose" apoptosis. In response, VCU teach that one agent alone (FP alone) had a minimal effect on apoptosis (see page 33, line 27 to page 34, line 3) and that the co-administration of a cyclin dependent kinase and a cellular differentiation agent (PMA and FP) resulted in a synergistic drug interaction (page 15, lines 16-21). It further teaches that its method involves co-administering to the cancer cells a cyclin dependent

kinase inhibitor and an agent that induces cellular differentiation. Several categories of agents that induce cellular differentiation may be utilized in the invention, including histone deacetylase inhibitors, such as suberoylanilide hydroxamic acid (SAHA). Examples of types of cancer cells in which apoptosis may be promoted by the invention are **leukemia ceils**, prostate cancer cells, breast cancer cells, multiple myeloma cells, and lymphoma cells (page 4, line 27 to page 5, line 9). Applicant states that claim 23 further recites that the cells are "exposed" to imatinib mesylate and SAHA for about 48 hours and states that the prior art does not address this limitation. In response, the instant specification teaches that the process of "contacting" the target cells is accomplished by "administering" a tyrosine kinase inhibitor and a histone deacetylase inhibitor to the subject (paragraph11). In the prior art, for both ALL and CML, Thiesing et al. teach administration of the tyrosine kinase inhibitor tyrosine kinase inhibitor, imatinib mesylate or STI571 and teach that it should be supplemented with another agent known to treat leukemia. Thiesing et al. does not teach supplementing STI571 with suberoylanilide hydroxamic acid. VCU teach administration of a histone deacetylase inhibitor with another agent known to treat leukemia and teach co-administration within the time range of 24-72 hours (page 11, lines 7-12) which overlaps and encompasses the claimed 48 hours. Applicant further asserts that the prior art does not teach a further limitation in that cancer cells are CML cells that are either accelerated phase or blast crisis phase. In response, Thiesing et al. teach that STI571 (imatinib mesylate) has shown significant activity in all phases of **CML** as well as Philadelphia chromosome positive acute leukemias (**ALL**) (also known as blast crisis

phase) (page 3195, 1st paragraph). Additionally, VCU teach co-administration a cellular differentiation agent (such as SAHA) to promote apoptosis in cancer cells in combination with another agent to treat leukemia, such as a cyclin dependent kinase inhibitor (see abstract). As stated in In re Kerkhoven, 626 F.2d 846, 205 USPQ 1069, at page 1072 (CCPA 1980):

> It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition which is to be used for the very same purpose. In re Susi, 58 CCPA 1074, 1079-80, 440 F.2d 442, 445, 169 USPQ 423, 426 (1971); In re Crockett, 47 CCPA 1018, 1020-21, 279 F.2d 274, 276-77, 126 USPQ 186, 188 (CCPA 1960). As this court explained in Crockett, the idea of combining them flows logically from their having been individually taught in the prior art.

Regarding the limitations of claim 27, argued separately, please see the response supra. Applicant states that Thiesing expressly states on page 3199 that the results of the study are applicable to chronic phase patients whose current treatment regimens include low-dose, continuous exposure to agents such as IFN and Ara-C. In response, as stated supra, Thiesing et al teach that **resistance would develop with long-term administration of STI571** and suggest the **combination** of STI571 with other agents to either prevent the emergence of resistant clones or to enhance the eradication of the leukemic clone (page 3199, columns 1-2). In both **ALL** and **CML**, Thiesing et al. teach that **STI571 should be supplemented with another agent known to treat leukemia**. VCU teach administration of a histone deacetylase inhibitor with another agent known to treat leukemia. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references.

See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Donna Jagoe whose telephone number is (571) 272-0576. The examiner can normally be reached on Monday through Friday from 8:00 A.M. - 4:30 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne (Bonnie) Eyler can be reached on (571) 272-0871. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/YVONNE L. EYLER/
Supervisory Patent Examiner, Art Unit 1619

Donna Jagoe /D. J./
Examiner
Art Unit 1619

May 18, 2010